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Evaluating Joint Effects of Induction-Salvage Treatment Regimes on Overall Survival in Acute Leukemia

Abdus S. Wahed[1] Peter F. Thall[2]

[1]Department of Biostatistics, University of Pittsburgh

[2]Dept. of Biostatistics, M.D. Anderson Cancer Center

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Outline

Collaborator

Peter F. Thall

Acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS)

- **AML/MDS** : Myeloid hematologic malignancies, i.e., blood cancers that originate in the bone marrow
- **Easy to Diagnose**: AML/MDS patients have too few normal, functional blood cells (red cells, T-cells, white blood cells, WBCs) and far too many blastic (undifferentiated) leukemia cells
- **Rapidly Fatal**: 35-50% five-year survival, depending mainly on age and type of cytogenetic abnormality.
- **Treatment Goal**: Kill the cancer cells, and bring the patient's normal blasts, platelets and WBCs back to functional levels.

Two Phases of Leukemia Treatment

Frontline or Remission Induction Therapy

- At the start: Chemotherapy (chemo) is given, to achieve a complete remission (CR), defined as:
  - Less than 5% blastic (undifferentiated) blood cells, and none with leukemic phenotype and
  - Platelet count $> 10^5/\mu$L and
  - WBC count $> 10^3/\mu$L

  based on a bone marrow biopsy.
- Achieving CR (quickly) is a necessary, but (unfortunately) not a sufficient condition to achieve long-term survival - - patients may (i) relapse after achieving CR, or (ii) die while in CR.

Two Phases of Leukemia Treatment

Maintenance or Salvage Therapy

- In chemotherapy of AML/MDS:
  - if the induction treatment does not achieve a CR, or
  - if a CR is achieved but the patient suffers a relapse, then

  a salvage treatment usually is given in a second attempt to achieve a CR.
- Salvage therapy may consist of another chemotherapy, usually different from that given as induction or, in some cases, a stem cell transplant (SCT).
- If CR is achieved, maintenance therapy (chemo or a SCT) may be given

Motivating Dataset from AML/MDS Trial

Induction Treatments (assigned through randomization)

- Fludarabine + cytosine arabinoside ("ara- C") + idarubicin (FAI)
- FAI + all-trans retinoic acid (ATRA, an acid form of vitamin A)
- FAI + granulocyte colony stimulating factor (G- CSF)
- FAI + ATRA + G-CSF.

Salvage Treatments (not randomly assigned)

- MANY different types of salvage were given. We classified them into two major groups: salvages containing high dose ara-C (HDAC) or not.

Analysis of AML/MDS Trial

Primary Analysis (Estey, Thall, and Pierce et al., 1999, *Blood*)

- **Primary scientific aim**: Assess the effects of adding ATRA, G-CSF, or both to FAI on the probability of success, defined as the patient being alive and in CR six months after the start of treatment.
- Analysis done using logistic regression, Kaplan-Meier plots, and Cox model regression.
- Based on the simplifying assumption that the only relevant treatments were the 4 frontline therapies. Salvage therapy was completely ignored.

Analysis of AML/MDS Trial

What if ...

- Patients in one induction arm are more treatment-resistant than those in other arms?
- Patients in the 4 induction arms receive salvages at different rates?
- One particular salvage treatment leads to longer overall survival?
- One particular salvage treatment leads to longer overall survival . . . but only among patients whose disease is resistant to induction?
- . . .

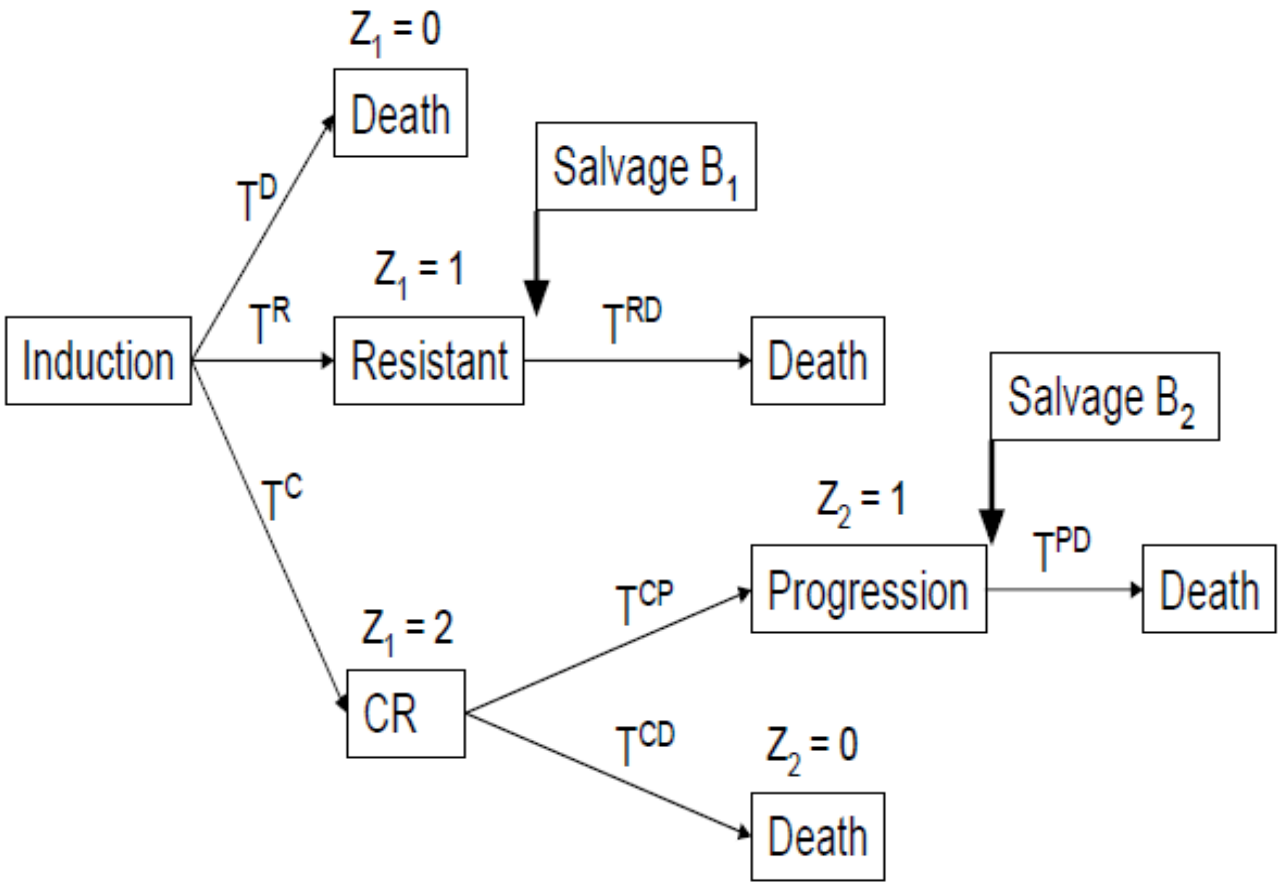
Analysis of AML/MDS Trial

Primary Motivation

- Ignoring salvage treatment might lead to biased estimation of induction treatment effects→ Must consider both induction and salvage
- Goal: Estimate induction-salvage treatment combination effects on overall survival→ Apply "Dynamic Treatment Regime" methods

Setting:

Treatments, States, and Sojourn Times in the AML/MDS Trial



Treatment Regimes

Regime (A, B_1, B_2)

Treat with induction therapy A, if the patient's disease becomes resistant to A treat with salvage B_1, or if relapse occurs after achieving complete remission treat with B_2.

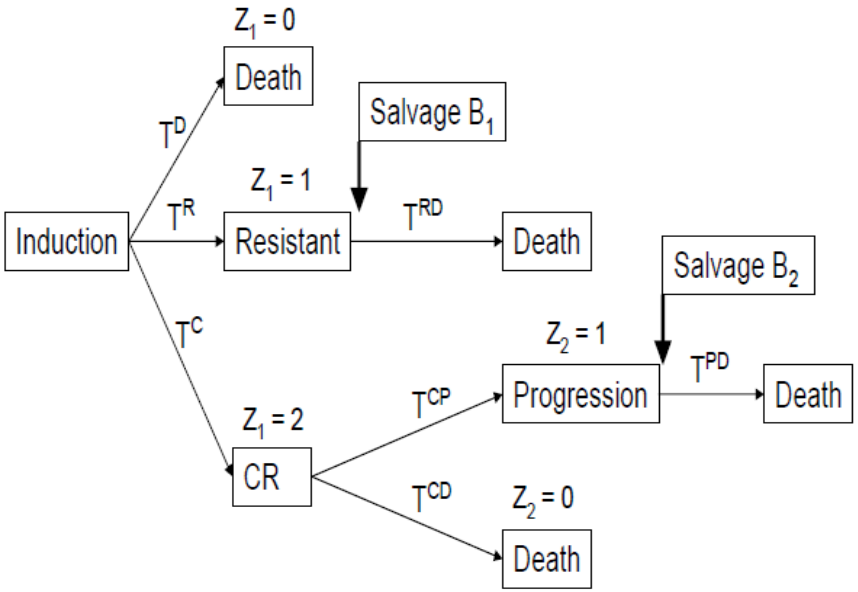
Regimes in AML/MDS Trial

A total of 16 treatment regimes (a, b_1, b_2), $a \in \{$FAI, FAI+G, FAI+ATRA, FAI+G+ATRA$\}$, $b_1, b_2 \in \{$HDAC, OTHER$\}$

Goal

Compare 16 regimes based on overall mean survival

Overall Survival



$$T = \begin{cases} T^D & \text{if } Z_1 = 0 \\ T^R + T^{RD} & \text{if } Z_1 = 1 \\ T^C + T^{CP} + T^{PD} & \text{if } Z_1 = 2 \text{ and } Z_2 = 1 \\ T^C + T^{CD} & \text{if } Z_1 = 2 \text{ and } Z_2 = 0 \ . \end{cases} \quad (1)$$

Censoring and Observed Data

Censoring

Since patients can be right-censored at any time during the study, any of these sojourn times are subjected to right censoring.

Observed Data

- Baseline covariates ($\mathbf{X_i}$), including induction treatment
- Intermediate response indicator (Z_{1i}) (0 for death before becoming resistant (1) or achieving CR (2))

Censoring and Observed Data

Observed Data

- Progression indicator for relapse (Z_{2i}) (1, if disease progresses, and 0 for no progression)
- Sojourn times U_i^j, $j \in \{D, R, C, RD, CD, CP, PD\}$ as appropriate, where $U_i^j = \min(T_i^j, C_i)$
- Stage-specific covariates including salvage treatment as appropriate

Likelihood

Contribution of a typical patient

$$\mathcal{L} = \mathcal{L}_1 \times \{\mathcal{L}_{2,RD}\}^{I\{Z_1=1\}} \times \{\mathcal{L}_{2,CD}\}^{I\{\mathbf{Z}=(2,0)\}} \times \{\mathcal{L}_{2,PD}\}^{I\{\mathbf{Z}=(2,1)\}} \tag{2}$$

Likelihood contribution for the first stage outcome

$$\mathcal{L}_1 = \Pi_{j\in\{D,R,C\}} \{f^j(T^0 \mid A)\}^{I(Z_1=j)\delta^j} \{\overline{F}^j(T^0 \mid A)\}^{1-\delta^j}. \tag{3}$$

Likelihood

Likelihood contribution of a patient who becomes resistant to treatment and dies/gets censored

$$\begin{aligned} \mathcal{L}_{2,RD} &= \{f^{RD|R}(U^{RD} \mid T^R, A, B_1)\}^{\delta^{RD}} \\ &\times \{\overline{F}^{RD|R}(U^{RD} \mid T^R, A, B_1)\}^{1-\delta^{RD}}. \end{aligned} \tag{4}$$

Likelihood contribution of patients who die in CR ($Z_2 = 0$)

$$\mathcal{L}_{2,CD} = \{f^{CD|C}(U^{CD} \mid T^C, A)\}^{\delta^{CD}} \{\overline{F}^{CD|R}(U^{CD} \mid T^R, A)\}^{1-\delta^{CD}} \tag{5}$$

Likelihood

Likelihood contribution of patients with disease progression $\mathbf{Z} = (2,1)$

$$\begin{aligned} \mathcal{L}_{2,PD} &= \{f^{PD|CP}(T^{PD,0} \mid T^{C}, T^{CP}, A, B_2)\}^{\delta^{PD}} \\ &\times \{\overline{F}^{PD|CP}(T^{PD,0} \mid T^{C}, T^{CP}, A, B_2)\}^{1-\delta^{PD}} \end{aligned} \quad (6)$$

Parametric models

Assume parametric models of the type

$$\ln T_i^j = \mathbf{X}_i \beta^j + \sigma^j \epsilon_i, \qquad \text{for} \quad i = 1, \ldots, n.$$

Maximum Likelihood

- Use maximum likelihood to estimate the parameters of the postulated models
- Use regular model fit statistics (AIC, BIC, etc.)to check model fits

Overall Mean Survival Under Regime $(A, B_1, B_2), \theta(A, B_1, B_2)$

$$
\begin{aligned}
& \int \Big\{ Pr(Z_1 = 0|A, X)\theta^D(A, X) + Pr(Z_1 = 1|A, X) \Big[\theta^R(A, X) \\
+ \quad & \int \theta^{RD}(A, B_1, X, X^{(R)}) d\mu(X^{(R)}) \Big] \\
+ \quad & Pr(Z_1 = 2|A, X) \Big\{ \theta^C(A, X) + \int \Big[Pr(Z_2 = 0|Z_1 = 2, A, X, X^{(C)}) \\
\times \quad & \theta^{CD}(A, X, X^{(C)}) + Pr(Z_2 = 1|Z_1 = 2, A, X, X^{(C)}) \Big(\theta^{CP}(A, X, X^{(C)}) \\
+ \quad & \int \theta^{PD}(A, B_2, X, X^{(C)}, X^{(P)}) d\mu(X^{(P)}) \Big) \Big] d\mu(X^{(C)}) \Big\} \Big\} d\mu(X) \qquad (7)
\end{aligned}
$$

Estimating Overall Mean Survival Under Regime $(A, B_1, B_2), \theta(A, B_1, B_2)$

- Estimate component means from the assumed parametric model fits
- Average over the empirical distribution of respective covariates to estimate $\theta(A, B_1, B_2)$
- Use bootstrap to estimate the variance of $\hat{\theta}(A, B_1, B_2)$

Inverse-probability-of-treatment-and-censoring-weighting

- Historically, inverse-probability-of-treatment-(and censoring)-weighting has been THE tool for constructing unbiased estimators for regime-specific means
- This is done,
  - first by identifying patients who received treatments consistent with the specific regime of interest.
  - next by weighting the uncensored failure times using censoring survival distribution and the probability of following the specific regime, and, lastly,
  - taking the weighted average of the failure times.

IPW Estimator

- For example, the IPTW estimates for regime-specific overall mean survival $\theta(A, B_1, B_2)$ is

$$\frac{\sum_{i=1}^{n} W_{AB_1B_2i} T_i}{\sum_{i=1}^{n} W_{AB_1B_2i}}, \tag{8}$$

$$W_{AB_1B_2i} = \frac{I_i(A)\delta_i}{\hat{K}(T_i)} \left\{ I(Z_{1i} = 0) + \frac{I(Z_{1i} = 1) I_i(B_1)}{\hat{Pr}(B_1 | Z_{1i} = 1, A, X_i, X_i^{(R)})} + \right.$$
$$\left. I(Z_{1i} = 2, Z_{2i} = 0) + \frac{I(Z_{1i} = 2, Z_{2i} = 1) I_i(B_2)}{\hat{Pr}(B_2 | Z_i = (2,1), A, X_i, X_i^{(C)}, X_i^{(P)})} \right\}. \tag{9}$$

(Analytical formula for variance estimator is available)

Analysis of AML/MDS Trial-First stage events

	Initial Outcomes Following Induction Therapy						
	Death		Resistant Disease		CR		Total
Group	N (%)	T^D	N (%)	T^R	N (%)	T^C	N
All Patients	69 (33)	$_{22}24_{32}$	39 (19)	$_{51}59_{70}$	102 (48)	$_{30}32_{34}$	210
FAI	17 (31)	$_{21}27_{52}$	17 (31)	$_{41}63_{97}$	20 (37)	$_{29}31_{44}$	54
FAI+ATRA	15 (28)	$_{18}22_{44}$	13 (24)	$_{55}59_{76}$	26 (48)	$_{29}31_{44}$	54
FAI+G	20 (38)	$_{22}32_{45}$	4 (8)	$_{27}77_{112}$	28 (54)	$_{29}36_{40}$	52
FAI+G+ATRA	17 (34)	$_{14}21_{30}$	5 (10)	$_{48}51_{70}$	28 (56)	$_{28}32_{38}$	50

Analysis of AML/MDS Trial-Second stage events

	Outcomes Following CR or Resistant Disease							
	Death After Res		Death in CR		Prog After CR		Death After Prog	
	N (%)	T^{RD}	N (%)	T^{CD}	N (%)	T^{CP}	N (%)	T^{PD}
All	37 (95)	$_{62}79_{148}$	9 (9)	$_{46}293_{345}$	93 (91)	$_{190}256_{329}$	83 (93)	$_{106}128_{175}$
HDAC	25 (93)	$_{27}65_{117}$	–	–	–	–	47 (89)	$_{62}98_{253}$
Other	12 (100)	$_{82}130_{252}$	–	–	–	–	36 (90)	$_{122}158_{191}$

Analysis of AML/MDS Trial-Model fits

Table: Bayesian information criterion (BIC).

Time to	Exp	Weibull	LLogist.	LNormal
death (T^D)	204.9	<u>197.4</u>	199.3	205.5
resistance (T^R)	108.7	65.9	63.1	<u>60.8</u>
CR (T^C)	247.5	131.3	<u>91.5</u>	92.6
death from resistance (T^{RD})	<u>157.5</u>	161.4	166.5	171.8
death from CR (T^{CD})	<u>28.0</u>	31.9	29.4	29.2
disease progression from CR (T^{CP})	271.2	259.3	<u>248.4</u>	251.8
death from disease progression (T^{PD})	288.9	297.0	284.9	<u>282.7</u>

Analysis of AML/MDS Trial-First-Stage Models

	Death	Resistance	CR
Intercept	$_{2.80}3.79_{4.80}$	$_{3.67}4.36_{5.05}$	$_{3.10}3.38_{3.65}$
Frontline			
FAI	$_{-0.15}0.29_{0.73}$	$_{-0.23}0.13_{0.50}$	$_{-0.13}0.05_{0.22}$
FAI+ATRA	$_{-0.40}0.08_{0.56}$	$_{-0.22}0.17_{0.57}$	$_{-0.21}-0.05_{0.11}$
FAI+G	$_{-0.29}0.23_{0.60}$	$_{-0.42}0.09_{0.59}$	$_{-0.11}0.05_{0.22}$
FAI+G+ATRA	ref	-	-
Age	$_{-0.02}-0.005_{0.01}$	$_{-0.016}-0.007_{0.002}$	$_{-0.0015}0.0023_{0.006}$
Cyto*			
0 vs. 2	$_{-0.57}-0.13_{0.30}$	$_{-0.22}-0.11_{0.43}$	$_{-0.22}-0.08_{0.05}$
1 vs. 2	$_{-0.57}-0.17_{0.24}$	$_{-0.13}0.04_{0.21}$	
σ	$_{0.54}0.65_{0.79}$	$_{0.30}0.38_{0.47}$	$_{0.15}0.17_{0.20}$

*0 = (“DIP,-Y”,“IM”), 1=“-5,-7”, 2=(“+8”, “11Q”, “INV16”, “T(8,21)”, “MISC”).

Analysis of AML/MDS Trial-Second-Stage Models

	T^{RD}	T^{CP}	T^{PD}
Intercept	$-6.31 - 1.32_{3.68}$	$6.49 8.11_{9.73}$	$-0.72 1.25_{3.23}$
Frontline			
FAI	$-0.57 0.64_{1.85}$	$-0.42 0.17_{0.76}$	$-0.86 - 0.21_{0.45}$
FAI+ATRA	$0.55 1.83_{3.10}$	$-0.28 0.29_{0.86}$	$-0.09 0.50_{1.09}$
FAI+G	$0.87 2.83_{4.80}$	$0.03 0.62_{1.21}$	$-0.30 0.27_{0.84}$
Cyto*			
0 vs. 2	$-0.77 0.29_{1.36}$	$-0.34 0.03_{0.41}$	$-0.56 - 0.05_{0.45}$
1 vs. 2	$-0.46 0.49_{1.44}$	$-0.95 - 0.52_{-0.10}$	$-0.90 - 0.32_{0.26}$
Age	$-0.05 - 0.01_{0.03}$	$-0.006 - 0.004_{0.014}$	$-0.04 - 0.03_{-0.01}$

Analysis of AML/MDS Trial-Second-Stage Models

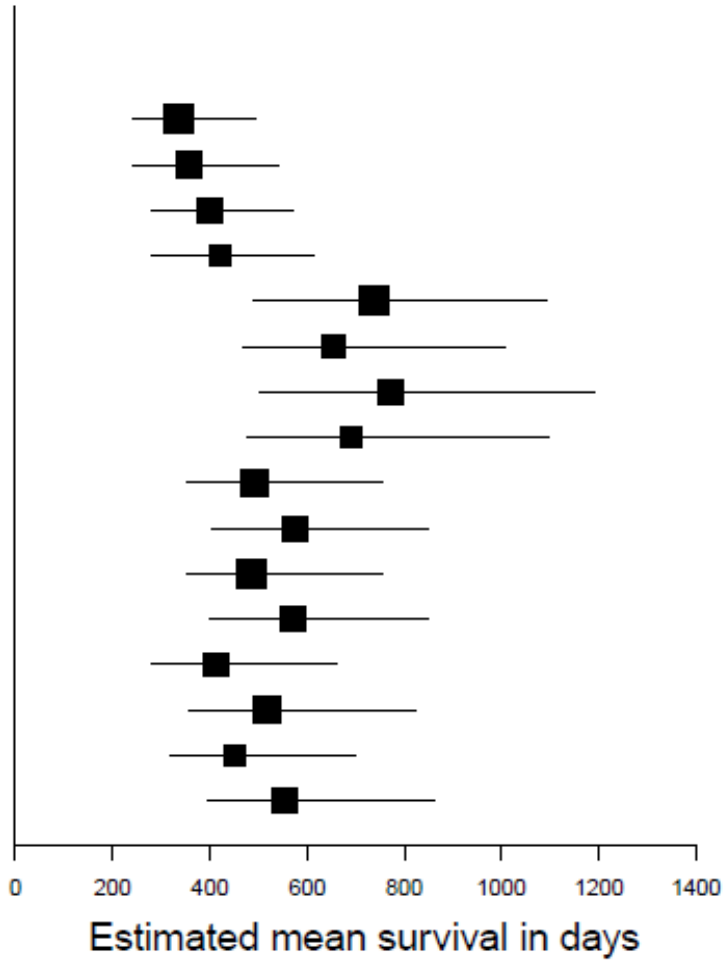
	T^{RD}	T^{CP}	T^{PD}
$\log T^R$	$_{0.11}1.20_{2.30}$	–	–
$\log T^C$	–	$_{-1.29}-0.83_{-0.37}$	–
$\log T^P$	–	–	$_{0.55}0.85_{1.16}$
Salvage			
HDAC	$_{-4.07}-1.61_{0.85}$	$_{-0.94}-0.34_{0.27}$	$_{-0.84}-0.39_{0.06}$
Interaction between induction and salvage therapy			
FAI×HDAC	$_{-2.31}0.28_{2.88}$	$_{-0.13}-0.80_{1.73}$	
[FAI+ATRA]×HDAC	$_{-0.99}1.66_{4.31}$	$_{-0.22}0.64_{1.51}$	
[FAI+G]×HDAC	$_{1.02}4.25_{7.48}$	$_{0.37}1.20_{2.03}$	
Scale		$_{0.34}0.40_{0.49}$	$_{0.85}0.99_{1.15}$

Analysis of AML/MDS Trial-Estimated Strategy Means

Strategy	IPTW	LB1	LB2
$(FAI\ ,\ HDAC\ ,\ HDAC)$	$_{149}189_{229}$	$_{220}281_{375}$	$_{242}335_{494}$
$(FAI\ ,\ HDAC\ ,\ OTHER\ )$	$_{129}258_{397}$	$_{207}289_{432}$	$_{241}357_{541}$
$(FAI\ ,\ OTHER\ ,\ HDAC)$	$_{162}214_{283}$	$_{261}346_{441}$	$_{281}400_{571}$
$(FAI\ ,\ OTHER\ ,\ OTHER)$	$_{147}275_{422}$	$_{248}354_{504}$	$_{280}422_{613}$
$(FAI+ATRA\ ,\ HDAC\ ,\ HDAC)$	$_{334}524_{751}$	$_{408}594_{864}$	$_{489}737_{1093}$
$(FAI+ATRA\ ,\ HDAC\ ,\ OTHER\ )$	$_{263}460_{707}$	$_{376}507_{710}$	$_{469}655_{1009}$
$(FAI+ATRA\ ,\ OTHER\ ,\ HDAC)$	$_{342}529_{749}$	$_{436}623_{922}$	$_{50}772_{1193}$
$(FAI+ATRA\ ,\ OTHER\ ,\ OTHER)$	$_{269}465_{713}$	$_{399}536_{763}$	$_{478}690_{1095}$
$(FAI+G\ ,\ HDAC\ ,\ HDAC)$	$_{251}337_{445}$	$_{309}406_{1151}$	$_{353}493_{757}$
$(FAI+G\ ,\ HDAC\ ,\ OTHER\ )$	$_{217}307_{408}$	$_{345}457_{1217}$	$_{404}577_{850}$
$(FAI+G\ ,\ OTHER\ ,\ HDAC\ )$	$_{253}338_{445}$	$_{306}400_{1151}$	$_{355}486_{755}$
$(FAI+G\ ,\ OTHER\ ,\ OTHER)$	$_{218}309_{410}$	$_{345}451_{1210}$	$_{402}569_{847}$
$(FAI+G+ATRA\ ,\ HDAC\ ,\ HDAC\ )$	$_{169}328_{514}$	$_{246}343_{528}$	$_{282}413_{661}$
$(FAI+G+ATRA\ ,\ HDAC\ ,\ OTHER)$	$_{215}294_{367}$	$_{285}396_{563}$	$_{356}517_{824}$
$(FAI+G+ATRA\ ,\ OTHER\ ,\ HDAC\ )$	$_{187}351_{546}$	$_{281}381_{569}$	$_{320}451_{700}$
$(FAI+G+ATRA\ ,\ OTHER\ ,\ OTHER)$	$_{236}318_{392}$	$_{324}434_{614}$	$_{395}554_{863}$

Analysis of AML/MDS Trial-Estimated Strategy Means

Strategy	n
(FAI, HDAC, HDAC)	42
(FAI, HDAC, OTHER)	37
(FAI, OTHER, HDAC)	37
(FAI, OTHER, OTHER)	32
(FAI+ATRA, HDAC, HDAC)	42
(FAI+ATRA, HDAC, OTHER)	35
(FAI+ATRA, OTHER, HDAC)	35
(FAI+ATRA, OTHER, OTHER)	28
(FAI+G, HDAC, HDAC)	40
(FAI+G, HDAC, OTHER)	36
(FAI+G, OTHER, HDAC)	40
(FAI+G, OTHER, OTHER)	36
(FAI+G+ATRA, HDAC, HDAC)	34
(FAI+G+ATRA, HDAC, OTHER)	37
(FAI+G+ATRA, OTHER, HDAC)	31
(FAI+G+ATRA, OTHER, OTHER)	34



Summary

- Developed likelihood-based method for analyzing survival data from two-stage treatment of leukemia
  - Separately models the state-specific sojourn times adjusting for covariates observed prior to entering the state
  - Uses inner structure of the data
  - Conditional inferences can be made about the state-specific sojourn times
  - Adjustment for post-baseline covariates are done separately for state-specific sojourn times
  - Inference for treatment regimes are done using boot-strap methods

Summary

- Analyzed a leukemia dataset using likelihood method and IPW method
  - Estimated regime-specific means are larger for likelihood-based methods compared to IPW method
  - However, qualitative ranking of treatment regimes are similar
  - Although, conditional inferences can be made about the state-specific sojourn times, often there are not enough observations to diligently fit component models, subjecting the inference to model mis-specification
  - Deriving analytical formula for variances is difficult, if not impossible, for likelihood-based method
  - It is not clear how to adjust for covariates (pre- and post-baseline) in the IPW setting

Contact Information

If you have any questions, please send an e-mail to:

Abdus S. Wahed
WahedA@edc.pitt.edu

Peter F. Thall
rex@mdanderson.org